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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/700,906 | 02/26/2001 | Hans-Dieter Flad | 661-50303 | 3318 |

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[REDACTED] EXAMINER

SCHULTZ, JAMES

[REDACTED] ART UNIT [REDACTED] PAPER NUMBER

1635

DATE MAILED: 12/18/2002

16

Please find below and/or attached an Office communication concerning this application or proceeding.

| | | | |
|------------------------------|-----------------|--------------|--|
| Office Action Summary | Application No. | Applicant(s) | |
| | 09/700,906 | FLAD ET AL. | |
| Examiner | Art Unit | | |
| J. Douglas Schultz | 1635 | | |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) Responsive to communication(s) filed on 06 November 2002.

2a) This action is FINAL. 2b) This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4) Claim(s) 1-15 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5) Claim(s) _____ is/are allowed. *Atw*

6) Claim(s) 1-15 is/are rejected.

7) Claim(s) ~~1-15~~ is/are objected to. *Atw*

8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) The proposed drawing correction filed on _____ is: a) approved b) disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.

12) The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) All b) Some * c) None of:
1. Certified copies of the priority documents have been received.
2. Certified copies of the priority documents have been received in Application No. _____.
3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.

14) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) The translation of the foreign language provisional application has been received.

15) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

| | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____. . |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____. . | 6) <input type="checkbox"/> Other: _____ |

Application/Control Number: 09/700,906
Art Unit: 1635

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DETAILED ACTION

Claim Objections

Claims 1-15 are objected to because of the following informalities: They are not grammatically correct sentences. The subject methods, medicaments, or processes lack a corresponding article. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 1-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

It is unclear from the grammar of said claims what the term "thereof" refers back to.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-8, and 10-13 provide for the use of oligonucleotides for the preparation of a medicament, but, since the claims do not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claims 1-8 and 10-13 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd. v. Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

It is noted that the closest prior art to the claims above is that of Schluter et al. (J. Cell Biol. 1993, 123(3) 513-522), who disclose the use of an antisense oligonucleotide to Ki-67 whereby the proliferation of cells is measured. However, this reference does not disclose a method or process of preparing a medicament derived from said oligo.

Claim 9 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for antisense-mediated inhibition of Ki-67 expression *in vitro*, does not reasonably provide enablement for antisense-mediated inhibition of Ki-67 expression *in vivo*, or for methods of treating diseases associated with its expression *in vivo*. The specification does not

enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The above invention is drawn to a pharmaceutical preparation to be used in the treatment of the whole animal having a condition associated with Ki-67, wherein said compositions are administered to animals such that the expression of Ki-67 is inhibited. The specification teaches a method of using the oligonucleotide that forms the active ingredient of the above claimed medicament to inhibit the expression of Ki-67 in cells *in vitro*.

The specification as filed does not provide any guidance or examples that would enable a skilled artisan to use the disclosed compounds or methods of using said compounds in *in vivo* environments. Additionally, a person skilled in the art would recognize that predicting the efficacy of an antisense compound *in vivo* based solely on its performance *in vitro* is highly problematic. Thus, although the specification prophetically considers and discloses general methodologies of using the claimed constructs *in vivo* or in methods of inhibition or treatment, such a disclosure would not be considered enabling since the state of antisense-mediated gene inhibition is highly unpredictable. The factors listed below have been considered in the analysis of enablement:

- (A) The breadth of the claims;
- (B) The nature of the invention;
- (C) The state of the prior art;
- (D) The level of one of ordinary skill;
- (E) The level of predictability in the art;
- (F) The amount of direction provided by the inventor;
- (G) The existence of working examples; and
- (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The following references are cited herein to illustrate the state of the art of treatment of the whole animal using antisense-mediated therapy.

A recent (2002) article by Braasch et al. emphasizes that major obstacles persist in the art: "gene inhibition by antisense oligomers has not proven to be a robust or generally reliable technology. Many researchers are skeptical about the approach, and it has been suggested that many published studies are at least partially unreliable" (Pg. 4503, para. 1 and 2). Braasch et al. goes on to identify factors that contribute to the unpredictable efficacy of antisense compounds *in vivo*: poor antisense oligonucleotide access to sites within the mRNA to be targeted, difficulties with delivery to and uptake by cells of the antisense oligos, toxicity and immunological problems caused by antisense oligos, and artifacts created by unpredictable binding of antisense compounds to systemic and cellular proteins.

Regarding the difficulties of predicting whether antisense oligonucleotides can access sites within their target mRNA, Braasch et al. explains, "it has been difficult to identify oligonucleotides that act as potent inhibitors of gene expression, primarily due to difficulties in predicting the secondary structures of RNA (Pg. 4503, para. 1 and 2). Branch adds that "internal structures of target RNAs and their associations with cellular proteins create physical barriers, which render most potential binding sites inaccessible to antisense molecules" (Page 45, third column). Additionally, in a review of the potential use of antisense oligos as therapeutic agents, Gewirtz et al. teach that the inhibitory activity of an oligo depends unpredictably on the sequence

and structure of the nucleic acid target site and the ability of the oligo to reach its target. (Page 3161, second and third columns).

The uptake of oligonucleotides by cells has been addressed by Agrawal, who states, “[o]ligonucleotides must be taken up by cells in order to be effective....several reports have shown that efficient uptake of oligonucleotides occurs in a variety of cell lines, including primary cells whereas other reports indicate negligible cellular uptake of oligonucleotides. Cellular uptake of oligonucleotides is complex process; it depends on many factors, including the cell type, the stage of the cell cycle, the concentration of serum. It is therefore, difficult to generalize that all oligonucleotides are taken up in all cells with the same efficiency” (Page 378). “[M]icroinjection or using lipid carriers to supply an oligonucleotide in cell culture increases the potency of the oligonucleotide in cell culture, but it is not clear how relevant this approach is for *in vivo* situations.” (Page 379).

Braasch et al. discuss the non-specific toxicity effects of *in vivo* antisense administration; “even when active oligomers are discovered, the difference in oligonucleotide dose required to inhibit expression is often not much different than doses that lead to nonselective toxicity and cell death... oligonucleotides can bind to proteins and produce artifactual phenotypes that obscure effects due to the intended antisense mechanism” (Pg. 4503, para. 1 and 2). Branch affirms that “non-antisense effects are not currently predictable, rules for rational design cannot be applied to the production of non-antisense drugs, These effects must be explored on a case by case basis” (Page 50), while Tamm et al. states that “[i]mmune stimulation is widely recognized as an undesirable side-effect...the immunostimulatory activity of a phosphorothioate-modified

oligonucleotide is largely unpredictable and has to be ascertained experimentally" (page 493, right column).

Further, Branch reasons that "the value of a potential antisense drug can only be judged after its intended clinical use is known, and quantitative information about its dose-response curves and therapeutic index is available" (Page 46, second column). Tamm et al. concludes by stating that until "the therapeutic activity of an antisense oligonucleotide is defined by the antisense sequence, and thus is to some extent predictable...antisense will not be better than other drug development strategies, most of which depend on an empirical approach."

The specification of the instant application fails to provide adequate guidance for one of skill in the art to overcome the unpredictability and challenges of applying results from *in vitro* experiments to the *in vivo* treatment of disease, as exemplified in the references above.

Furthermore, one skilled in the art would not accept on its face the examples given in the specification of the inhibition of Ki-67 expression *in vitro* as being correlative or representative of the successful *in vivo* treatment of any and/or all conditions or diseases suspected of being associated with Ki-67 expression. This is particularly true in view of the lack of guidance in the specification and known unpredictability associated with the efficacy of antisense in treating or preventing any conditions or disease suspected of being associated with a particular target gene *in vivo*. The specification as filed fails to provide any particular guidance which resolves the known unpredictability in the art associated with appropriate *in vivo* delivery and treatment effects provided by antisense administered, and specifically regarding the instant composition as claimed.

Finally, the quantity of experimentation required to practice the invention as claimed *in vivo* would require the *de novo* determination of formulations with low toxicity and immunogenicity that are successfully delivered, and most importantly, that target sites in appropriate cells and /or tissues harboring Ki-67 expression such that all harmful expression is inhibited, that healthy expression is permitted appropriately *in vivo*, and further, that treatment and/or preventive effects are provided for any and/or all diseases or conditions suspected of being associated with Ki-67 expression *in vivo*. Since the specification fails to provide any guidance for the successful treatment or prevention of any and/or all diseases or conditions suspected of being associated with Ki-67 expression in humans, or their tissues or cells, and since resolution of the various complications in regards to targeting a particular gene in an organism is highly unpredictable, one of skill in the art would have been unable to practice the invention over the scope claimed using the methods presented in the specification without engaging in undue trial and error experimentation.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

- (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 14 is rejected under 35 U.S.C. 103(a) as being anticipated by any of Schluter et al., (J. Cell. Biol. (1993) 123(3) 513-522), Maeshima et al. (J. Am. Soc. Nephrology. 1995. 7(10) 2219-2229) or Duchrow et al. (Arch. Imm. Ther. Exp. 1995. 43(2) 117-21), in view of Baracchini et al. (U.S. Patent Number 5,801,154).

Claims 14 is drawn to an oligonucleotide that hybridizes with the mRNA that codes for Ki-67.

The references of Schluter et al., and Maeshima et al. both teach oligonucleotides that hybridize with the mRNA that codes for Ki-67. Duchrow et al. teach the cDNA sequence encoding Ki-67.

Duchrow et al. do not teach antisense sequences that target Ki-67.

It would have been obvious to one of ordinary skill in the art to modify the antisense compounds of Schluter et al. or Maeshima et al. to comprise sequences between 22 and 46 nucleotides long, because Schluter et al. teach an anti-Ki-67 sequence 21 nucleotides long, and Maeshima et al. teach an anti-Ki-67 sequence 18 nucleotides long, and because extending these

lengths to 22 nucleotides simply constitutes a design choice that does not affect the inhibitory activity so long as the proper sequence, taught by Duchrow et al., is used. Further, it would have been obvious to use the cDNA sequence of Duchrow et al. to generate antisense sequences as taught by Baracchini et al. for inhibition of Ki-67 expression. One would have been motivated to create such compounds because Schluter et al. and Maeshima et al. teach that Ki-67 controls cellular proliferation that may be involved in tumor formation or kidney disorders respectively. Finally, one would have a reasonable expectation of success given that Schluter et al. and Maeshima et al. both teach antisense-mediated inhibition of Ki-67, and because Baracchini et al. teach that antisense inhibition of known sequences *in vitro* is routine to one of ordinary skill in the art.

Thus in the absence of evidence to the contrary, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Allowable Subject Matter

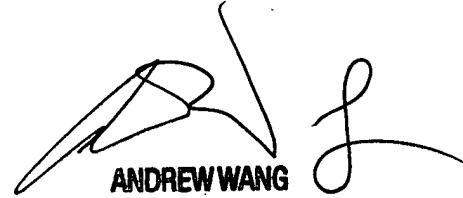
Claim 15 would be allowable if rewritten to overcome the rejection(s) under 35 U.S.C. 112, second paragraph, set forth in this Office action and to include all of the limitations of the base claim and any intervening claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Douglas Schultz whose telephone number is 703-308-9355. The examiner can normally be reached on 8:00-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on 703-308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

James Douglas Schultz, PhD
December 17, 2002



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